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EXAMINER	
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ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,715	BRESCIANI ET AL.	
	Examiner	Art Unit	
	CARALYNNE HELM	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 16-21* is/are pending in the application.

4a) Of the above claim(s) *16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Note to Applicant: References to paragraphs in non-patent literature refer to full paragraphs (e.g. 'page 1 column 1 paragraph 1' refers to the first full paragraph on page 1 in column 1 of the reference)

Election/Restrictions

To summarize the restriction, applicant elected Group I for prosecution. Claims 16-21 were withdrawn from further consideration.

Response to Arguments

In light of the amendment to claim 9 the rejection under 35 USC 112, second paragraph is hereby withdrawn.

Applicant's arguments, filed July 29, 2008, with respect to the rejection under 35 USC 102(b) of claims 10-15 have been considered but are moot in view of the new grounds of rejection.

Applicant's arguments, filed July 29, 2008, with respect to the rejection under 35 USC 103(a) of claims 1-9 have been considered but are not persuasive. The arguments presented are focused on Lai et al. and Carli et al. as well as present unexpected results.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As detailed in the previous action and below, Lai et al. teach a method of treating a cross-linked polymer with pure supercritical fluid that is envisioned for use in drug delivery devices. Carli et al. teach a method of loading a drug into a cross-linked polymer by contacting t he polymer with a drug dissolved in a supercritical fluid, then subsequently removing the supercritical fluid. One of ordinary skill in the would have found it obvious to combine these references since the method of drug loading was known at the time of the invention and Lai et al. explicitly teach the use of their materials to deliver drugs

In response to applicant's argument of unexpected results, section 716.02(c) of the MPEP states that, "whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.'" Here applicant has highlighted data that describes results of three experimental runs with a single cross-linked polymer, two NSAID drugs and slightly different processing conditions. The arguments regarding this data compare the invention to a supercritical fluid drug loading reference process with no pre-treatment step. The unexpected results favoring the invention were a higher rate of loading, an increase in drug content, and a decrease in the crystallinity of the loaded drug. There is

a vast array of cross-linked polymers, linked by physical or chemical cross links that can be loaded with drugs. These polymers run the spectrum from crystalline to rubbery amorphous, but applicant has only shown data for a single glassy amorphous polymer. There are also larger molecular weight drugs, DNA and proteins which are also considered drugs, as well as inorganic and salt forms of drugs. Applicant has only demonstrated a small molecular weight base and acid. Berens et al. (Journal of Applied Polymer Science 1992 46:231-242) teach that the ability of a polymer to be infused by a drug/additive varies greatly depending on the particular combination of drug/additive and polymer since this process is dependent on the drug's/additive's solubility in and interaction with the polymer (see page 239 column 1 paragraph 3, column 2 paragraphs 1-2 and table IV). Applicant's selected processing conditions are not reflected in the claims, so it is not clear that the same phenomenon of unexpected results discussed could be extrapolated to other processing conditions. Therefore the data is not commensurate in scope with the claims.

The data presented by applicant gives a narrow snapshot of the products resulting from the application of their claimed method. Example 1 and example 2 utilize the same supercritical fluid at the same temperature and pressure for the experimental and reference samples. These examples only differ in the drug that was loaded into the polymer and both show an increase in the amount of drug loaded using applicant's method as compared to the reference method that has no pre-treatment step. Interestingly the percent difference between the loading produced by applicant's method and the reference for the two examples were quite different totaling 13% in example 1

and 52% in example 2. Although example 3 also showed higher loading using applicant's method, the no pre-treatment reference method used supercritical fluid at a lower temperature and pressure. In addition, example 3 used a different supercritical fluid than examples 1 and 2. Domingo et al.(Journal of Supercritical fluids 2001 21:147-157) teach that for a given time period, a higher temperature and pressure result in a higher loading of a solute in a polymer via supercritical fluid treatment (see figure 2). Depending on the polymer and solute, a 10 degree difference in the temperature of the supercritical fluid could result in a 23% change in loading (see figure 2c - benzoic acid in silica gel sample- black triangles). Thus the 23% percent difference shown for example 3 is not as instructive or demonstrative as it initially seems. This also means that some processing conditions (e.g. temperature, pressure, and particular supercritical fluids) do not yield a different result when comparing the claimed method with its no pre-treatment reference.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

Claims 8 and 10 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals, such as cross-linked cellulose and cross-linked starch which meet the written description and enablement provisions of 35 USC 112, first paragraph. However, claims 8 and 10 are directed to encompass derivatives, which only correspond in some undefined way to specifically instantly disclosed chemicals. None of these derivatives meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed derivatives, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence. Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v.*

> *American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the above chemically structurally defined chemicals, but not the full breadth of the claims meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claims 1 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Regarding claim 1, the disclosure teaches that pure supercritical fluid is used in the pre-treatment step (see instant specification page 3 lines 4-5). No discussion is provided permitting the use of “substantially pure” supercritical fluid in this step or the maximum amount of impurities encompassed by such a supercritical fluid preparation. Regarding claim 9, the disclosure provides no discussion of the point of comparison for the “increase” in nanocrystalline and amorphous drug present in the product due to the practice of the claimed process.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the process where the loaded drug is in amorphous form in a larger proportion than before it was loaded into the polymer, does not reasonably provide enablement for the process where the loaded drug is in amorphous and nanocrystalline form. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Applicant gives ample direction as to how the process is practiced such that amorphous drug is impregnated into the treated polymer. In contrast, there is no guidance or teaching provided that demonstrates the presence of both amorphous and nanocrystalline drug in the polymer upon application of the claimed method. In fact, two of the three examples provided indicate that no nanocrystalline drug is present in the polymer due to the practice of the method (e.g. 0% drug crystallinity). The third example provides no discussion of the type of crystalline structure that is impregnated into the polymer upon application of the claimed method. Kazarian et al. (International Journal of Pharmaceutics 2002 232:81-90), like examples 1 and 2, teach the contacting of a drug containing solution of supercritical carbon dioxide with a polymer to impregnate polyvinylpyrrolidone with ibuprofen (see page 85 column 1 paragraph 1-column 2 line 5). They also teach that the drug is molecularly dispersed within the polymer with no crystalline structure present (amorphous) (see page 86 column 1 paragraph 1-column2 line 5). It is possible that the particular supercritical fluid used in the process (carbon dioxide vs. ethylene) plays a

major role in the crystallinity of the drug impregnated into the polymer. Nevertheless, there is not ample guidance provided to enable one of ordinary skill in the art to practice the claimed method such that the amount of amorphous and nanocrystalline drug in the polymer is higher than that dissolved in the supercritical fluid.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "substantially" in claim 1 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since the term is not defined that actual amount of purity required for the supercritical fluid used in the method is not known.

Applicant recites a listing of "cross-linked" polymers in claims 8 and 10. Included in this listing is cyclodextrin. The compound cyclodextrin itself is not a cross-linked polymer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The four factual inquires of Graham v. John Deere Co. have been fully considered and analyzed in the rejections that follow.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai et al. (U.S. Patent No. 6,670,454) in view of Carli et al. (WO 99/25322- see IDS).

Lai et al. teach a method where a cross-linked biodegradable polymer is treated with a pure supercritical fluid (see abstract and claim 12; instant claim 1). Specifically, Lai et al. teach that the cross-linked polymers can be polysaccharides, as well as ordinary synthetic polymers (see column 3 lines 38-48; instant claim 8). In a particular embodiment, the cross-linked polymer is taught to be treated with pure supercritical carbon dioxide for 1 hour (see column 5 lines 18-21; instant claims 1-3 and 7). Although, Lai et al. teach that the supercritical fluid treated cross-linked polymers of their invention are useful as drug delivery systems, they do not teach the steps necessary to produce such a device (see column 4 lines 38-39).

Carli et al. teach a method of impregnating a cross-linked polymer with a drug (making a drug delivery system) using a supercritical fluid (see abstract; instant claim 1). Specifically, Carli et al. teach the steps where the drug is dissolved in the supercritical fluid, then the cross-linked polymer is contacted with this drug containing fluid impregnating the polymer with the drug, then the supercritical fluid is removed resulting in a drug loaded cross-linked polymer (see page 2 lines 6-10; instant claim 1). Carli et al. go on to teach that the contacting of the drug loaded supercritical fluid can occur via a static and/or dynamic process for 15 minutes to 24 hours (see page 2 lines 22-26 and line 31-page 3 line 3; instant claims 4-6). The particular supercritical fluids taught for use in the process of Carli et al. include carbon dioxide, ethylene, propylene, and nitrous oxide (see page 2 lines 15-19; instant claim 7). Further, Carli et al. teach a collection of cross-linked polymers suitable for their process which include cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose (interpreted as

cross-linked cellulose), cross-linked sodium starch glycolate (interpreted as cross-linked starch), cross-linked polystyrene, and cross-linked acrylic acid, all of which fall into the categories of those taught by Lai et al. (see page 3 lines 17-22; instant claim 8). The technique of drug impregnation with a supercritical fluid was recognized as part of the ordinary capabilities of one skilled in the art. As a result, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of Carli et al. with that of Lai et al., where the specific polymers taught by Carli et al. are used in the invention of Lai et al. Lai et al. in view of Carli et al. do not specifically teach that the drug precipitates inside the cross-linked polymer nor the nature (amorphous character) of the drug. However, applicant's disclosure on page 2 of the specification states that the method of Carli et al. was employed by the applicant and the desired characteristics (amorphous character) of the drug within the cross-linked polymer was attained (see instant specification page 2 lines 7-9 and 15-17). Further, since the method of impregnating the polymer with the drug taught by Carli et al. is the same as that claimed, the resulting structure would have the same properties as those claimed present in the result of the claimed method. Thus the teachings of Lai et al. in view of Carli et al. meet the limitations of impregnated drug recited in instant claims 1 and 9. Therefore claims 1-9 are obvious over Lai et al. in view of Carli et al.

Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lai et al. in view of Samain et al. (US Patent No. 5,736,371)

Lai et al. teach a method where a cross-linked biodegradable polymer is treated with a pure supercritical fluid (see abstract and claim 12; instant claim 10). In addition, Lai et al. teach the cross-linking and subsequent treatment of the cross linked polymers. Specifically, Lai et al. teach that the cross-linked polymers can be polysaccharides, as well as ordinary synthetic polymers (see column 3 lines 38-48; instant claim 10). In a particular embodiment, the cross-linked polymer is taught to be treated with pure supercritical carbon dioxide for 1 hour (see column 5 lines 18-21; instant claims 11-14). Although, Lai et al. teach that the supercritical fluid treated cross-linked polymers of their invention are useful as drug delivery systems, Lai et al. do not teach starch or cellulose as particular polysaccharides.

Samain et al. teach biodegradable polymers envisioned for use in drug delivery (see column 1 lines 6-8). Samain et al. go on to teach cross-linked cellulose and starch as particular biodegradable polymers of the invention (see column 2 lines 64-66; instant claim 10). Since Samain et al. teach that cross-linked cellulose and starch are known for use in drug delivery devices and Lai et al. teach a method of making cross-linked polysaccharides as well as a method of preparing them for use in drug delivery devices, it would have been obvious to one of ordinary skill in the art at the time of the invention to select cellulose or starch as the polysaccharide for the method of Lai et al. Therefore claims 10-14 are obvious over Lai et al. in view of Samain et al.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Thursday 8-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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